ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

LOTEMAX™
(Loteprednol Etabonate)
0.2% Ophthalmic Suspension
NDA 20-803

Pharmos Corporation

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
(HFD-550)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-803

Lotemax™

(Loteprednol Etabonate)

0.2% Ophthalmic Suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Lotemax™, PHARMOS Corporation has prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(b)(3)*, which evaluates the potential environmental impact of the manufacture, use and disposal of the product.

Loteprednol Etabonate is a chemically synthesized drug which is administered as a sterile ophthalmic suspension in treatment of the signs and symptoms of seasonal allergic conjunctivitis of the eye. The drug substance is made at SIPSY, Avrille', France and the drug product is manufactured by Bausch & Lomb, Tampa, Florida. The finished drug product will be used mainly by patients in their homes.

Loteprednol Etabonate may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Drug product that expires, or is returned from the field will be separated from the packaging and disposed of as a non-hazardous substance at a licenced facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal

quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

4/24/97
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

4/24/97
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1998
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
	MAR 04 1998
DIVISION ASSIGNED	NUMBER ASSIGNED

MEGA DOC PAK

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314.101)*

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmos Corporation	March 3, 1998
ADDRESS *(Number, Street, City, State and ZIP Code)*	**TELEPHONE NO.** *(Include Area Code)*
33 Wood Ave, South Suite 466 Iselin, NJ 08830	732 603 3526
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* 20-803

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Loteprednol etabonate	Alrex

CODE NAME *(If any)*	CHEMICAL NAME
Loteprednol etabonate 0.2% Loteprednol etabonate allergy Core 353	See package insert

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS (S)
Sterile Suspension	Ophthalmic	0.2%

PROPOSED INDICATIONS FOR USE

For the treatment of the signs and symptoms of seasonal allergic conjunctivitis

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

Pharmaceutical Division | 8500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

ORIGINAL

BAUSCH & LOMB
Healthcare and Optics Worldwide

February 6, 1997

NC
NEW CORRESP

Joanne Holmes
Project Manager
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: DESK COPIES
NDA 20-803
Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Dear Ms. Holmes:

As requested, enclosed are 10 desk copies of Volume 1.1 and one desk copy of the environmental assessment for the recently submitted NDA 20-803. Also enclosed is a computer diskette containing the package insert in both Word and Word Perfect and two sets of four computer diskettes containing the requested information for each of the four clinical studies submitted in the NDA.

Please let Anna Wysowskyj know if you have any comments or questions about these enclosures. She can be reached by telephone at 813/975-7775 or by fax at 813/975-7757.

Best Regards,

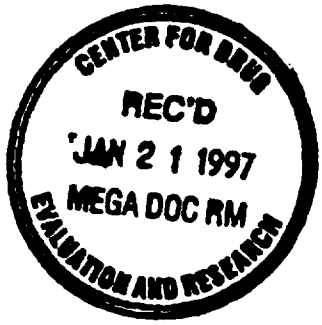
Christine Simmons

Christine Simmons, Pharm.D
Director, Regulatory Affairs

ORIGINAL

2 Innovation Drive
Alachua, FL 32615
TEL 904-462-1210
904-462-5401

PHARMOS



NEW CORRESPONDENCE

January 10, 1997

Joanne Holmes
FDA, Division of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products
HFD 550
9201 Corporate Blvd.
Rockville, MD

RE: NDA 20-803

Dear Ms. Holmes:

This letter provides confirmation that, the following personnel listed below at Bausch & Lomb Pharmaceuticals are authorized by Pharmos to contact the FDA on all prior and future issues concerning the above referenced NDA.

Christine Simmons, Director, Regulatory Affairs
Cal Bowman, Vice President, Regulatory Affairs
Ellen Strahlman, M.D., Director of Corporate Medical Affairs

The purpose of this authorization is to facilitate the interchange of data and regulatory information on this program between B & L Pharmaceuticals and the FDA, without the necessity of referencing Pharmos each time.

If you have any questions, please do not hesitate to contact me at 904-462-1210 (phone) or 904-462-5401 (fax).

Sincerely,

G. Riesenfeld

Gad Riesenfeld, Ph.D.
Executive Vice President
Chief Operating Officer

GR/amm

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO
CSO INITIALS DATE

Holmes
550

NDA 20-803

FEB 12 1997

Pharmos Corporation
Attention: C. Christine Simmons, Pharm. D.
Director, Regulatory Affairs
2 Innovation Drive
Alachua, FL 32615

Dear Dr. Simmons:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Therapeutic Classification: Standard

Date of Application: January 31, 1997

Date of Receipt: February 3, 1997

Our Reference Number: 20-803

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 4, 1997, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

Lissante C. LoBianco
Acting Supervisor Consumer Safety Officer
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-803
HFD-550/Div. Files
HFD-550/Clin Rev/Holmes
HFD-550/SPMS/LoBianco
DISTRICT OFFICE

Drafted by: jh/February 10, 1997/20803.ack

ACKNOWLEDGEMENT (AC)

Pharmaceutical Division
Tampa FL 33637
Fax 813 975 7770

ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

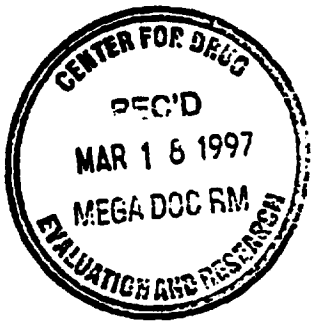
BAUSCH & LOMB
Healthcare and Optics Worldwide

B2

ORIG AMENDMENT

March 17, 1997

Wiley Chambers, MD
Acting Director
Division of Ani-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville MD 20850



Re: **Amendment to Sections 2, 3, 8, and 10 of NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Dear Dr. Chambers:

As requested by Joanne Holmes, Clinical Reviewer, Pharmos Corporation amends NDA 20-803 with the following:

NDA Section 2:

Disclosure Statement - All safety data from all sources available to the sponsor, U.S. and non-U.S., are included in the application. Loteprednol etabonate is not marketed in any country in any dosage form, so there are no relevant data on marketed product.

Safety Cut-Off Date - The cut-off date for reporting of data from clinical trials is March 1996.

NDA Section 3:

CMC Section in Electronic Format - All portions of the CMC section which are currently available in electronic format are provided on the enclosed diskette. A hard copy of the contents of the diskette is also provided *(Attachment 1)*

In addition, the sponsor amends the application by adding the following statement to the Stability Commitment:

Expiration Dating - Following approval of this NDA, the expiration date of the drug product may be extended based on real time data meeting the requirements of the stability protocols included in NDA Section 3.2.9.3.

NDA Sections 8 and 10:

The case report forms for studies 143 and 144 have been annotated to include the coresponding SAS codes as they appear on the diskettes sent to you on February 6, 1997.

If you have any questions regarding this submission, please call Anna Wysowskyj at (813) 975-7700 ext. 7192.

Sincerely,

Anna B Wysowskyj for

Chris Simmons, PharmD
Director Regulatory Affairs

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

ORIGINAL

BAUSCH & LOMB
Healthcare and Optics Worldwide

April 15, 1997

Wiley Chambers, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville MD 20850

BC
ORIG AMENDMENT

Re: **Amendment to Section 3 of NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Dear Dr. Chambers:

As requested by Joanne Holmes, Clinical Reviewer, Pharmos Corporation amends Section 3 of NDA 20-803 with additional CMC information regarding the following:

Sampling
In-Process Testing
Filling Operation
Particulates in Packaging Components

If you have any questions regarding this submission, please call Anna Wysowskyj at (813) 975-7700 ext. 7192.

Sincerely,

Anna Wysowskyj

Christine Simmons, PharmD
Director Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

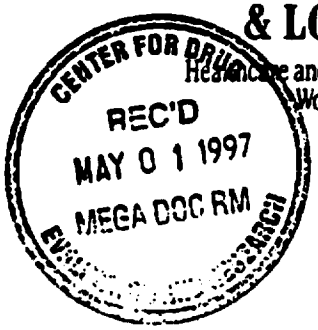
CSO INITIALS DATE

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

ORIGINAL

V

BAUSCH & LOMB
Healthcare and Optics Worldwide



NC
NEW CORRESP

April 30, 1997

Wiley Chambers, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville MD 20850

Re: **NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
Amendment to Pending Application: Trade Names

Dear Dr. Chambers:

Pharmos Corporation amends NDA 20-803 to include two proposed trade names for loteprednol etabonate ophthalmic suspension, 0.2% (see attachment). The original application did not include trade name information for this product.

If you have any questions regarding this submission, please call Anna Wysowskyj at (813) 975-7700 ext. 7192.

Sincerely,

Anna B. Wysowskyj for

Christine Simmons, PharmD
Director Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

January 13, 1998

ORIGINAL

A2
ORIG AMENDMENT

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Product
HFD-550
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-803
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
NDA Amendment

Dear Dr. Chambers:

We wish to amend NDA 20-803 by incorporating by reference the amendments submitted to NDA 20-583 on December 10, 1997 and December 11, 1997.

If you have any questions regarding this letter, please contact me at 813/975-7775.

Best Regards,

Christine Simmons, Pharm.D
Vice President, Regulatory Affairs

Pharmaceutical Division | 8500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

January 14, 1998

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550
***Attention:* Document Control Room**
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-583
Loteprednol Etabonate Ophthalmic Suspension, 0.5%
NDA Amendment

NDA 20-803
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
NDA Amendment

Dear Dr. Chambers:

We wish to amend NDA 20-583 (loteprednol etabonate ophthalmic suspension, 0.5%) and NDA 20-803 (loteprednol etabonate ophthalmic suspension, 0.2%) with the attached information which was faxed to you on January 9, 1998. The faxed information responded to five CMC questions which were faxed by FDA to Bausch & Lomb on January 8, 1998. A copy of the fax containing the five CMC questions is also provided for your reference. All volume and page number references refer to the December 10, 1997 NDA amendment.

If you have any questions regarding this letter, please contact me at 813/975-7775.

Best Regards,

Christine Simmons

Christine Simmons, Pharm.D
Vice President, Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-803

JAN 16 1998

Bausch & Lomb
Attention: Christine Simmons, Pharm.D.
Vice President, Regulatory Affairs
8500 Hidden River Parkway
Tampa, Florida 33637

Dear Dr. Simmons:

We acknowledge receipt on January 14, 1998, of your January 13, 1998, amendment to your new drug application for Alrex® (loteprednol etabonate ophthalmic suspension), 0.2%.

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is May 3, 1998.

If you have any questions, please contact Lissante C. LoBianco, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

WAC 1/16/98

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
[redacted] NDA 20-803
HFD-550/Div. Files
HFD-550/LoBianco/Chambers/Fenselau 1/16/98
DISTRICT OFFICE
Drafted by: lobianco/January 16, 1998/
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HFD-105
REVIEW EXTENSION

Pharmaceutical Division | 8500 Hidden River Parkway Tampa FL 33637 | 813 975 7700 Fax 813 975 7770

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Healthcare and Optics Worldwide

ORIGINAL

January 16, 1998

Wiley Chambers, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, **HFD-550**
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville MD 20850

Re: **NDA 20-803**
Loteprednol Etabonate Ophthalmic Suspension, 0.2%
Microbiology

Dear Dr. Chambers:

PHARMOS Corporation amends NDA 20-803 with the attached information regarding the sterility test method for loteprednol etabonate ophthalmic suspension, 0.2%.

If you have any questions regarding this submission, please call Anna Wysowskyj at (813) 975-7700 ext. 7192.

Sincerely,

Anna Wysowskyj

Anna Wysowskyj
Sr. Manager Regulatory Affairs
Bausch & Lomb Pharmaceuticals, Inc.

BAUSCH
& LOMB
Healthcare and Optics
Worldwide

DUPLICATE

February 26, 1998

BL

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-803
Alrex™ (loteprednol etabonate ophthalmic suspension), 0.2%
Revised Draft Labeling

Dear Dr. Chambers:

Enclosed are four copies of revised draft labeling for Alrex™. This labeling incorporates changes to the following sections of the labeling:

Clinical Pharmacology
Contraindications
Warnings
Carcinogenesis, mutagenesis, impairment of fertility
Pregnancy

If you have any questions regarding this submission, please call me at (813) 975-7727.

Best Regards,

Anna B. Wysocky for

Christine Simmons, PharmD
Vice President, Regulatory Affairs, Bausch & Lomb Pharmaceuticals, Inc.
Authorized Agent for PHARMOS Corporation

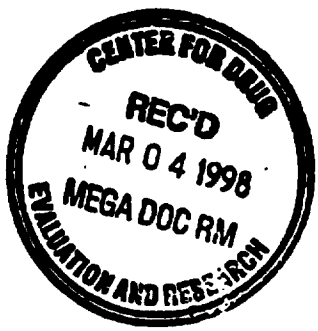
Tampa FL 33637 Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

BL

ORIG AMENDMENT

DUPLICATE



March 3, 1998

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-803
Alrex™ (loteprednol etabonate ophthalmic suspension), 0.2%
Draft Labeling Change

Dear Dr. Chambers:

We would like to amend NDA 20-803 with a change to the last paragraph of the Adverse Reactions section of the draft labeling submitted on February 26, 1998. A description of the revision is attached.

If you have any questions regarding this submission, please call me at (813) 975-7727.

Best Regards,

Anna B. Wyposky

Christine Simmons, PharmD
Vice President, Regulatory Affairs, Bausch & Lomb Pharmaceuticals, Inc.
Authorized Agent for PHARMOS Corporation

Pharmaceutical Division
8500 Hidden River Parkway
Tampa FL 33637
813 975 7700
Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

March 6, 1998

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-803
Alrex™ (loteprednol etabonate ophthalmic suspension), 0.2%
Revised Draft Labeling

Dear Dr. Chambers:

Enclosed are four copies of revised draft labeling for Alrex™. This labeling incorporates the changes described in the fax we received from you today.

If you have any questions regarding this submission, please call me at (813) 975-7727.

Best Regards,

Anne B. Wypinski for

Christine Simmons, PharmD
Vice President, Regulatory Affairs, Bausch & Lomb Pharmaceuticals, Inc.
Authorized Agent for PHARMOS Corporation

Tampa FL 33637
813 975 7700
Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

March 9, 1998

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD-550
Attention: Document Control Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: Amendment
NDA 20-803
Alrex (loteprednol etabonate ophthalmic suspension, 0.2%)
Revision to Package Insert

Dear Dr. Chambers:

Enclosed is a revised page 3 of 5 of the Alrex package insert sent to you on March 6, 1998. The only changes made to the 3-6-98 package insert are corrections of the multiples of the maximum clinical dose identified in the Carcinogenesis and Pregnancy sections of the insert. The corrections reflect the 0.2% loteprednol etabonate concentration of Alrex.

If you have any questions about this information, I can be reached at 813/975-7775.

Best regards,

Christine Simmons

Christine Simmons, Pharm.D
Vice President, Regulatory Affairs